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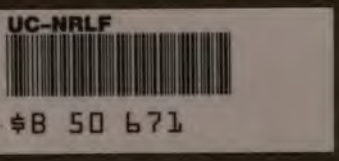

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THE METHYLATION OF PARA-AMINOPHENOL BY MEANS OF FORMALDEHYDE

BY

ERNEST CARL WAGNER

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The Methylation of p-Aminophenol by Means of Formaldehyde

A Study of Certain Methods for the Conversion of the Condensation-products of Formaldehyde and p-Aminophenol into N-Methyl-p-aminophenol

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This paper is divided as follows:

I– The Condensations of Formaldehyde and Aromatic Amines

A. Condensations in Neutral or Alkaline Media

B. Condensations in Acid Media

C. Summary of Important Condensations and Secondary Reactions

II– Methylation of Aromatic Amines by Means of Formaldehyde

III– Experimental Results on the Methylation of p-Aminophenol by Means of Formaldehyde

IV– Summary

I. The Condensations of Formaldehyde and Aromatic Amines

In the condensations of formaldehyde with the amines, the fundamental change consists in the splitting out of the elements of water, with the result that a methylene-group is introduced. Typically the necessary hydrogen atoms are displaced from an amino-group, or from two imino-groups. It is characteristic of certain condensations, however, that only nuclear hydrogen atoms are involved. The course of the condensation depends upon (a) the nature of the medium in which condensation occurs, *i.e.*, whether neutral, alkaline, or acid, (b) the relative proportions of amine and aldehyde, (c) the presence of substances with which further reaction may occur, and (d) the influence of substituent groups present in the amine molecule.

With respect to these influences, it can be said introductorily that what may be termed the normal condensation occurs in neutral or alkaline solution, that which results in presence of acid being essentially different. The relative amounts of amine and aldehyde present determine whether one or two amine molecules will be involved in the condensation, and also, when an excess of amine-salt is present, whether or not further condensations of the primary product with uncondensed amine will occur.

The influence of substituent groups upon aldehyde condensations was observed by Eibner[1] who found that trichloraniline did not react with chloral, though less chlorinated anilines condensed. In other cases, such as o-dimethyltoluidine, a condensing agent (zinc chloride) may be required.[2] It has been found also that tribromaniline does not condense with formaldehyde, either under ordinary conditions, or in a sealed tube at 250°. The effect of the substituent bromine-atoms in this case is so strong that the action of an excess of bromine upon a benzol solution of anhydroformaldehydeaniline not only brominates the aromatic nucleus, but to a certain extent eliminates the methylene-group previously united with the nitrogen-atom. This is evidenced by the appearance of tribromaniline as a constant product of this bromination.

A—Condensations of Formaldehyde and Aromatic Amines in Neutral or Alkaline Media.

The essential reactions which may occur, depending upon the nature of the amine, and upon the relative proportions of amine and formaldehyde, are the following:

(a) $C_6H_5.NH_2 + OCH_2 = C_6H_5.N{:}CH_2 + H_2O$
(anhydroformaniline)

(b) $\begin{matrix} C_6H_5NH \\ C_6H_5NH \end{matrix}\!\!>\!CH_2 + H_2O$
(methylene-di-phenamine base)

(c) $\begin{matrix} C_6H_5 \\ R \end{matrix}\!\!>\!N\!-\!\begin{matrix} H \\ H \end{matrix}\!\!>\!CH_2 + H_2O$
(methylene-di-phenamine base)

[1] *Annal.*, **302**, 349.
[2] Alexander, *Ber.*, **25**, 2408 (1892).

Compounds of these types are more or less generally referred to as "Schiff's Bases," which include also the condensation-products of other aldehydes.

The earliest known and simplest formaldehyde condensation of type (a) among aromatic amines was studied by Pratesi and Tollens[3] in the case of aniline. Anhydroformaldehydeaniline, or anhydroformaniline, is thus obtained in the trimeric form $(C_6H_5N.CH_2)_3$.[4] Polymerization occurs also with other amines, such as the toluidines[5] and p-aminophenol.[6] The existence of two forms of such compounds, having different melting points and solubilities, has been observed in several cases. This was attributed at first to different degrees of polymerization. It was shown by Bischoff, however, that $(CH_3.C_6H_4.N.CH_2)_n$ exists in two forms, both of which have the same molecular weight, corresponding to the formula $(CH_3.C_6H_4.N.CH_2)_3$. He concluded that the two forms must be geometrical isomers of the *cis* and *trans* types with respect to the $CH_3.C_6H_4$–groups attached to the $[=N.CH_2-]_3$ ring. Anhydroformaniline likewise probably exists in two forms. Dimeric forms of these anhydro-bases, such as

$$(CH_3.C_6H_4.N.CH_2)_2,$$

or structurally, $CH_3.C_6H_4.N<\begin{matrix}CH_2\\CH_2\end{matrix}>N.C_6H_4.CH_3$,

have been reported.[7]

The general reaction of which the formaldehyde-aniline condensation serves as a type was soon applied to the toluidines, etc., by Wellington and Tollens,[8] and has since that time been extended, where applicable, to apparently all amines of importance, both aliphatic and aromatic, as well as to many heterocyclic compounds.

[3] Pratesi, *Gazz. chim. ital.*, 14, 351 (1884); Tollens, *Ber.*, 17, 653 (1884); 18, 3309 (1885).

[4] Miller and Plöchl, *Ber.*, 25, 2020, (1892); Bischoff, *Ber.*, 31, 3248 (1899).

[5] Bischoff. *l. c.*

[6] D. R. P., 68707.

[7] *Ber.*, 31, 2037, 3248; *Annal.*, 256, 288.

[8] *Ber.*, 18, 3298 (1885).

Condensation of two equivalents of amine and one of formaldehyde is of type (b), and yields methylene-di-imine compounds of the type-formula $Ar.NH.CH_2.NH.Ar$. Thus two molecules of aniline and one of formaldehyde form methylenediphenyldi-imine, or dianilinomethane:[9] $C_6H_5.NH.CH_2.NH.C_6H_5$. By boiling this compound in alcohol, it is transformed into anhydroformaniline.[10] Exactly analogous condensations occur with other amines.[11]

The most interesting reaction of the di-imine bases occurs when they are heated with amine-salts. Diamino-diphenylmethane derivatives are thus formed, by a rearrangement which recalls the transformation of hydrazobenzene to benzidine:[12]

$$Ar.NH.CH_2NH.Ar. \longrightarrow Ar.NH.CH_2.Ar.NH_2$$
$$\longrightarrow NH_2.Ar.CH_2.Ar.NH_2.$$

As these compounds are formed directly when condensation is conducted in presence of free acid, and with base in excess of formaldehyde, the secondary reaction just given belongs more properly to Section B, where its probable mechanism will be indicated.

Condensations of types (a) and (b) may occur simultaneously, one or the other predominating; excess of aldehyde favors the first, while excess of amine favors the second.[13]

Condensations of type (c) are characteristic of secondary amines, and are in no essential manner different from the preceding. The methyltoluidines, for example, condense with formaldehyde to form $(C_7H_7.N.CH_3)_2CH_2$.[14] When heated with amine-salts, these compounds, like those obtained from primary amines, are rearranged to form dialkylamino-diphenylmethane derivatives.

Compounds intermediate between the methylene-di-imine bases ($Ar.NH.CH_2NH.Ar.$), and the diamino-diphenylmethanes

[9] Pratesi, Bischoff, *l. c.*

[10] Eberhardt and Welter, *Ber.*, **27**, 1804 (1894).

[11] Eibner, *Annal.*, **302**, 349 (1898): Bischoff, *l. c.*; Bischoff and Reinfeld, *Ber.*, **36**, 41 (1903); D. R. P. 138393, etc.

[12] D. R. P. 63081, 107718.

[13] Eibner; Eberhardt and Welter, *l. c.*

[14] Braun, *Ber.*, **41**, 2145 (1908).

($NH_2.Ar.CH_2.Ar.NH_2$), *viz.*, the aminobenzylanilines ($NH_2.Ar.CH_2.NH.Ar.$), are formed when an anhydroformaldehyde-base is heated with an amine-salt:[15]

$$C_6H_5.N{:}CH_2 + H.C_6H_4.NH_2(HCl) \rightarrow C_6H_5.NH.CH_2.C_6H_4.NH_2(HCl).$$

Condensations of nuclear-substituted amines proceed often in the normal manner; o-nitraniline, for example, yields

$$\left(\left[C_6H_4\begin{matrix}NO_2\\NH\end{matrix}\right]_2CH_2.\right)^{16}$$

Similar condensations occur with halogenated amines, aminobenzoic acids, aminosulphonic acids, benzidine, tolidine, phenetidine, etc.

It is of great practical importance that the methylene-group of the diphenylmethane compounds can be condensed with a third amine-molecule by oxidation, forming triphenylmethane derivatives, among which fuchsine and the homologous pararosanilines are included.[17]

Primary condensation-products of the type $Ar.N{:}CH_2$, although probably cyclic polymers devoid of double bonds, are able to unite, by addition, with several substances, the most important of which are (1) hydrogen, (2) sulphurous acid or bisulphites, and (3) hydrocyanic acid. These additions occur according to the following equations:[18]

(1) $Ar.N{:}CH_2 + 2H = Ar.NH.CH_3$

(2) $Ar.N{:}CH_2 + NaHSO_3 = Ar.NH.CH_2SO_3Na$

(3) $Ar.N{:}CH_2 + HCN = Ar.NH.CH_2.CN$

The bisulphite compound contains a replaceable $-SO_3H$ or $-SO_3Na$ group:[19] by interaction with cyanide a phenylglycinenitrile results:

$$Ar.NH.CH_2.SO_3Na + NaCN = Ar.NH.CH_2.CN + Na_2SO_3.$$

The synthesis of phenylglycine and its homologues is thus possible

[15] D. R. P. 87934.

[16] Pulvermacher, *Ber.*, 25, 2764;26, 955.

[17] D. R. P. 53937, 55565, 61146, 67013, 73092.

[18] Miller and Plöchl, *Ber.*, 25, 2020 (1892); Eibner, *Annal.*, 316, 89 (1901); Lepetit, *Atti. accad. Lincei*, 26, I, 126 (1917); *Gazz. chim. ital.*, 47, I, 197 (1917); *C. A.*, 1918, 366.

[19] Knoevenagel, *Ber.*, 37, 4073 (1904).

by a convenient method, as the products may be obtained directly by proper treatment of amine, cyanide, formaldehyde, and alkali.[20]

Preparation of phenylglycine-o-carbonic acid is accomplished by a similar process, starting with anthranilic acid.[21] Condensations of formaldehyde with anthranilic acid or its esters have been rather carefully studied.[22]

Union of the anhydro-base $Ar.N:CH_2$ with hydrocyanic acid or bisulphite may take place either after isolation of the base, or in a mixture of amine, formaldehyde, and cyanide or bisulphite. In the latter case it is to be supposed that the cyanhydrin or aldehyde-bisulphite is primarily formed, and reacts with the amine:

$$CH_2O + HCN \rightarrow CH_2\langle^{OH}_{CN} + H|N.H.Ar \rightarrow Ar.NH.CH_2.CN + H_2O$$

$$CH_2O + NaHSO_3 \rightarrow CH_2\langle^{OH}_{SO_3Na} + H|NH.Ar \rightarrow Ar.NH.CH_2.SO_3Na + H_2O.$$

The corresponding bisulphite compound of p-aminophenol is $HO.C_6H_4.NH.CH_2.SO_3Na$. It may be made either by dissolving the condensation-product $HO.C_6H_4.N:CH_2$ in bisulphite solution,[23] or by dissolving p-aminophenol in formaldehyde- bisulphite solution. The addition-product readily evolves sulphur dioxide when heated with acids, and may therefore be represented as a loose compound of the formula $(HO.C_6H_4N:CH_2)NaHSO_3$. Its alkaline solution exhibits reducing properties, and it has been recommended as a photographic developer under the name "Eurekin." The general similarity of this compound and the developer "Metol," as shown by the formulas

[20] *Ber.*, **27**, 1805; **39**, 987; D. R. P. 135332, 145376, etc.

[21] D. R. P. 117924, 120105, 158090, 151538.

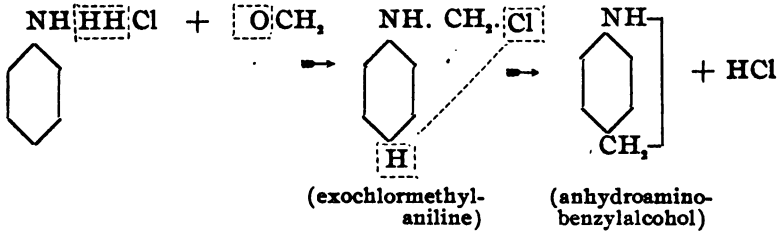
[22] Erdmann, *J. pr. Ch.*, (2), **63**, 387, 569; Mehner, *ib.*, (2), **63**, 244; **65**, 533; Goldschmidt, *Chem. Ztg.*, **26**, 179; Haller and Fiesselmann, *Annal.*, **324**, 118; Bischoff and Reinfeld, *Ber.*, **35**, 3440; **36**, 41.

[23] D. R. P. 68707.

$(p\text{-}HO.C_6H_4N:CH_2)NaHSO_3$, (Eurekin) $(p\text{-}HO.C_6H_4.NH.CH_3)_2H_2SO_4$, (Metol)
seems to be of little significance in the preparation of the latter.

B—Condensations of Formaldehyde and Aromatic Amines in Acid Media.[24]

The condensation of aniline and formaldehyde in presence of hydrochloric acid yields a chlorinated product $C_6H_5.NH.CH_2Cl$.[25] This compound is itself of no great importance, but derives interest from the fact that it readily loses a molecule of hydrochloric acid, especially in contact with alkalies, and passes into the anhydride of p-aminobenzyl alcohol:



These reactions occur strikingly in the case of methylaniline,[26] the exochlormethyl-derivative of which separates as white needles when the secondary base is allowed to stand with formaldehyde in dilute hydrochloric acid solution. The product, when treated, in solution, with alkali, is transformed into white, amorphous anhydro-p-methylamino-benzylalcohol. Analogous reactions occur also with ethylaniline[27] and other primary and secondary amines. That anhydroaminobenzylalcohol is a para-compound is shown by its reduction to p-toluidine.[28] The anhydroaminobenzylalcohols are characterized by their insolubility in water and in the usual

[24] D. R. P. 53937, 70402, 95184, 95600, 96851, 96852, 97710; *Ber.*, 31, 1037 (1891)); 33, 250 (1901); *C. C.*, 1898, II, 159; 1912, II, 2070; 1906, I, 1416; *C. A.*, 11, 582 (1917.)

[25] Goldschmidt, *Chem. Ztg.*, 24, 284 (1900); D. R. P. 96851; *cf.* Raikow, *Chem. Ztg.*, 20, 307 (1896).

[26] Goldschmidt, *l. c.*

[27] Goldschmidt, *Chem. Ztg.*, 26, 606, (1902).

[28] D. R. P. 83544.

organic solvents; they are soluble in dilute hydrochloric or other mineral acid, with formation of the corresponding salt. The anhydro-alcohols derived from primary amines are themselves secondary amines, and form nitrosamines. The anhydroaminobenzylalcohols are obtained in more or less polymerized condition, the degree of polymerization varying with the amount of acid present during their formation.[29] The simplest member is obtained in polymerized form from the true alcohol, $NH_2.C_6H_4.CH_2OH$, by heating with acid,[30] as well as by treatment of exochlormethylaniline, $C_6H_5.NH.CH_2Cl$, with alkali.

The anhydroaminobenzylalcohols may be prepared also from condensation-products of the types $Ar.N:CH_2$ and $(Ar.NH)_2CH_2$ by action of strong acids. Thus anhydroformaniline, in contact with strong hydrochloric acid, is gradually transformed into exochlormethylaniline, which is converted by alkali to anhydro-p-aminobenzylalcohol.[31] By action of glacial acetic acid in the cold, however, an isomeric form of anhydroformaniline results, having the probable formula $C_6H_5NH.CH_2C_6H_4.N:CH_2$,[32] and possessing the ability for further condensations.

Typical condensations occur with β-phenylhydroxylamine,[33] and with p-substituted amines such as p-toluidine, xylidenes, and p-chloraniline.[34] The products resemble the other anhydroaminoalcohols; that from p-chloraniline is exceptional in being crystallizable. In the same way p-aminophenol yields an amorphous base of the probable formula,[35]

$$HO.C_6H_4<\begin{matrix}NH\\|\\CH_2\end{matrix}$$

This differs from the anhydroaminobenzylalcohols mentioned above by its solubility in alkalies as the phenolate; it is precipitated from acid solution by sodium carbonate.

[29] D. R. P. 96851.
[30] D. R. P. 83544.
[31] D. R. P. 95184.
[32] D. R. P. 121506.
[33] D. R. P. 87972.
[34] D. R. P. 122474.
[35] Orloff, "*Formaldehyde*," Leipzig, (1909) p. 95.

With salts of aromatic amines, the anhydroaminobenzylalcohols combine to form diphenylmethane derivatives, a reaction of importance:[36]

$$C_6H_4<\begin{matrix}NH\\|\\CH_2\end{matrix} + H.C_6H_4.NH_2(HCl) \rightarrow C_6H_4<\begin{matrix}NH_2\\CH_2\end{matrix}>C_6H_4.NH_2(HCl).$$

By use of nuclear-substituted and N-alkylated amines, unsymmetrically substituted diphenylmethane derivatives may be obtained.

It will be recalled that diphenylmethane derivatives are formed (page 4) in another way, by heating the methylenedi-imine bases with excess of amine-salt, or with amine and acid, a transformation like that of hydrazobenzene to benzidine:

$$Ar.NH.CH_2.NH.Ar. \rightarrow Ar.NH.CH_2.Ar.NH_2 \rightarrow NH_2.Ar.CH_2.Ar.NH_2.$$

This transformation has been studied for o-nitraniline by Meyer and Rohmer,[37] and for several secondary amines by Braun.[38] It appears that the exochlor-compound is first formed, with splitting-off of a molecule of amine. The former may then pass into the anhydroaminobenzylalcohol, reaction of which with the amine first liberated yields the diphenylmethane compound which constitutes the end-product. For the simplest case the transformation may be indicated by the scheme:

$$\begin{matrix}C_6H_5NH\\C_6H_5NH\end{matrix}>CH_2 \xrightarrow{(2\,HCl)} C_6H_5.NH.CH_2.Cl \rightarrow C_6H_4<\begin{matrix}NH\\|\\CH_2\end{matrix}$$

$$C_6H_5.NH_2.HCl \qquad \downarrow$$

$$C_6H_4<\begin{matrix}NH_2\\CH_2\end{matrix}>C_6H_4.NH_2.$$

This general process is susceptible of many modifications. It is most simply carried out in a single operation, by interaction of formaldehyde and excess of amine in presence of acid. When mixed products are desired, the di-imine is first produced, and is further condensed with the salt of another amine.

[36] D. R. P. 96762.
[37] *Ber.*, 33, 250 (1901).
[38] *Ber.*, 41, 2145 (1908.)

The same products may be obtained in still another way, from the p-aminobenzylaniline derivatives, $NH_2.Ar.CH_2.NH.Ar$,[39] which are formed by interaction of amine-salts with bases of the type $Ar.N:CH_2$ (pages 4 and 5). The p-amino-benzylaniline thus obtained, when heated with amine and hydrochloric acid, yields a diphenylmethane derivative, with elimination of a molecule of amine:

$$NH_2.C_6H_4.CH_2.NH.C_6H_5 + H.C_6H_4.NH_2(HCl) \rightarrow NH_2.C_6H_4.CH_2.C_6H_4.NH_2(HCl) + C_6H_5.NH_2.$$

The anhydroaminobenzyl (or homologous) alcohols show a characteristic reaction with β-arylhydroxylamines, by which result the p-amino-benzaldehydes:

$$C_6H_5.NHOH + \begin{matrix} NH \\ | \\ CH_2 \end{matrix} > C_6H_4 \rightarrow C_6H_5.N:CH.C_6H_4.NH_2$$

$$\xrightarrow{(H_2O)} C_6H_5.NH_2 + OHC.C_6H_4.NH_2.$$

The same products are obtained by suitable reduction of nitro-compounds in neutral solution and in presence of formaldehyde.

While the secondary amines condense with formaldehyde in the normal manner, by virtue of the presence of amino-hydrogen, the tertiary amines show a different behavior. Dimethylaniline, condensed with formaldehyde in acetic acid solution, yields tetramethyldiaminodiphenylmethane,

$$(CH_3)_2N.C_6H_4.CH_2.C_6H_4.N(CH_3)_2.$$[40]

The m-aminophenols, and the corresponding cresols, react in the same way.[41] By dehydration and oxidation, the products of such condensations yield the pyronines.[42]

The m-diamines condense similarly to form diphenylmethane derivatives, from which acridine compounds are obtainable by loss of ammonia and by oxidation.[43] The o-diamines yield imidazole compounds.[44]

[39] D. R. P. 87934, 104230, 105797, 108064, 109498.

[40] Möhlau and Heinze, *Ber.*, 35, 359 (1902); *cf.* Pinnoff, *Ber.*, 27, 3166 (1894).

[41] D. R. P. Anm., 5528; D. R. P. 58955, 75373; *Ber.*, 27, 1894 (1894); *J. pr. Ch.*, 54, 217 (1896).

[42] D. R. P. 59003, 63081, 75138, 84988, 99613.

[43] Orloff, "*Formaldehyde*," Leipzig, 1909, pp. 97, 115-123, gives a general account, together with some of the numerous patents.

[44] O. Fischer, *Ber.*, 25, 2711; 32, 245.

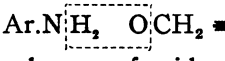
Amines of the naphthalene series condense with formaldehyde in acid solution with elimination of ammonia and water. Double junction between two naphthalene nuclei at their α and β positions is effected through a $-CH_2-$ and an $-NH-$ group. When, however, the β-position is occupied, as by $-SO_3H$, the amino-group is not involved, but the two nuclei are united through $-CH_2-$ attached at the 4-positions.[45]

It will not be profitable to extend further the list of condensations, though it is not even approximately complete. A brief and fairly comprehensive survey of the subject (up to about 1908) is given by Orloff.[46] Later work is recorded in the academic and patent literature.

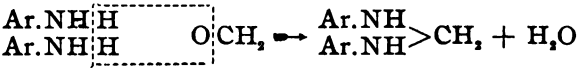
C—Summary of Important Condensations of Formaldehyde and Aromatic Amines.[47]

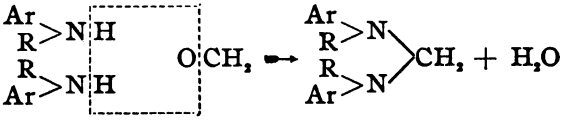
(1) *Primary Condensations*

(a) In absence of acids, one molecule of formaldehyde and one molecule of primary amine react to form readily polymerized N-methylene-amines (anhydro-formaldehydeamines):



(b) In absence of acids, one molecule of formaldehyde and two molecules of primary or secondary amine react to form methylene-di-imino bases (methylene-diphenamines, dianilinomethanes):





(c) Tertiary amines condense to form diphenylmethane derivatives:

[45] Morgan, *Proc.*, 16, 131; 195, 132 (1897); *J. C. S.*, 77, 814; 73, 536; Reed, *J. pr. Ch.*, 35, 298; Bucherer and Seide, *Ber.*, 40, 859; Senier and Austin, *J. C. S.*, 91, 1233; D. R. P. 84379.

[46] *l. c.* pp. 81-123.

[47] *Cf.* Friedländer, V. p. 5.

$$\begin{matrix} R_2N.Ar.H \\ R_2N.Ar.H \end{matrix} + O{:}CH_2 \rightarrow \begin{matrix} R_2N.Ar \\ R_2N.Ar \end{matrix}{>}CH_2 + H_2O$$

(d) In presence of acids, one molecule of amine and one of formaldehyde unite to form (in the case of HCl) the exochlormethylamino-compounds, which are converted by loss of hydrochloric acid into the reactive anhydroaminobenzyl alcohols. These are para-compounds, unless the para-position is initially occupied, in which case analogous compounds result with the $-CH_2-$ group otherwise disposed:

$$Ar.NH.H.HCl + O{:}CH_2 \xrightarrow{-H_2O} Ar.NH.CH_2Cl \xrightarrow{-HCl} Ar{<}\begin{matrix} NH \\ | \\ CH_2 \end{matrix}$$

(2) *Secondary Condensations*

(a) The anhydroformaldehyde-amines unite with amine-salts in the cold to form p-aminobenzylaniline derivatives:

$$Ar.N{:}CH_2 + H.Ar.NH_2(HCl) \rightarrow Ar.NH.CH_2.Ar.NH_2(HCl).$$

(b) The p-aminobenzylanilines unite with amine-salts in acid medium, and at higher temperatures, forming diphenylmethane derivatives, with elimination of a molecule of amine:

$$\begin{matrix} Ar.NH.CH_2.Ar.NH_2 \\ NH_2.Ar.H. \end{matrix} \rightarrow \begin{matrix} Ar.NH_2 \\ NH_2.Ar.CH_2.Ar.NH_2 \end{matrix}$$

(c) The methylenedi-imine bases, when heated with amine-salts, pass into corresponding diphenylmethane derivatives by rearrangement:

$$Ar.NH.CH_2.NH.Ar. \rightarrow NH_2.Ar.CH_2.NH.Ar \rightarrow NH_2.Ar.CH_2.Ar.NH_2.$$

(d) The anhydroaminobenzylalcohols react with amine salts to form diphenylmethane derivatives:

$$Ar{<}\begin{matrix} NH \\ | \\ CH_2 \end{matrix} + H.Ar.NH_2(HCl) \rightarrow Ar{<}\begin{matrix} NH_2 \\ CH_2 \end{matrix}{-}Ar.NH_2$$

II. Methylation of Aromatic Amines by Means of Formaldehyde

Among the aromatic amines, the time-honored method of alkylation employs the alkyl halides. Much more convenient than this method, however, is that in which an alkyl sulphate, and especially methyl sulphate, is the active agent.[48] This method is coming into increasingly wide use, because of the activity of methyl sulphate, and because of the relative simplicity of the operations. The methylation of p-aminophenol to N-methyl-p-aminophenol may be accomplished by this means, which is probably that by which the process is now conducted commercially. Methylation may be effected similarly by the use of the methyl ester of p-toluene-sulphonic acid.[49]

Other methods for conversion of primary to secondary amines include the following:

(1) Action of methyl alcohol in presence of concentrated sulphuric acid.[50]

(2) Hydrogenation of Schiff's bases catalytically, in presence of nickel[51] or metallic oxides.[52]

(3) Alkylation of primary to secondary amines through action of alkyl iodides upon Schiff's bases.[53] This method involves intermediate formation of unstable quaternary compounds by addition of alkyl iodides to bases of the type R.N:CHR'. The quaternary salts, by hydrolysis, yield secondary amine and aldehyde:

$$\mathrm{R.N{:}CHR' + R''I \longrightarrow \begin{matrix} R \\ R'' \end{matrix}\!\!>\!N{:}CH.R'} \quad (\mathrm{I})$$

$$\mathrm{(I) \xrightarrow{H_2O} \begin{matrix} R \\ R'' \end{matrix}\!\!>\!NH + CHO.R' + HI}$$

[48] Ullman, *Annal.*, **327**, 164 (1903); Meldola and Hallely, *J. C. S.*, 1912T, 912; Werner, *J. C. S.*, **105**, 2762 (1914); Havas and Guyot, *Chem. Ztg.*, **37**, 812; Shepard, *J. A. C. S.*, **38**, 2507 (1916); Klemenc and Edhoffer, *Monats.*, **38**, 553 (1918.)

[49] Ullmann and Wenner, *Annal.*, **327**, 120 (1903); Weyl, "*Methoden*," *II*, 1269 (1911.)

[50] D. R. P. 288825.

[51] Maihle, *Bull. Soc. chim.*, **25**, 321 (1919).

[52] E. P. 124219.

[53] Decker and Becker, *Annal.*, **395**, 362.

Among the secondary amines prepared by this method are methyl- and ethyl-aniline from benzylidine-aniline, and methyl-p-toluidine from benzylidine-p-toluidine.

(4) Condensation of primary amine and phenol.[54] N-methyl-p-aminophenol may be prepared in this way from hydroquinone and methylamine:

$$HO.C_6H_4.OH + NH.H.CH_3 \rightarrow HO.C_6H_4.NH.CH_3 + H_2O$$

A somewhat similar method involves the interaction of p-chlor-phenol and methylamine:[55]

$$HO.C_6H_4.Cl + H.NH.CH_3 \rightarrow HO.C_6H_4.NH.CH_3 + HCl$$

These methods are more properly described as arylations of aliphatic amines than as alkylations of aromatic amines, though this distinction has no significance so far as concerns the products.

Consideration of the several primary condensation-products of formaldehyde and the aromatic amines suggests four ways in which the introduced methylene-group might be changed to a methyl-group:

(1) Hydrogenation of the anhydroformaldehyde-amines:

$$Ar.N:CH_2 + 2H \rightarrow Ar.NH.CH_3$$

(2) Reduction of the exochlormethyl-amines obtained by condensation in acid solution:

$$Ar.NH.CH_2Cl + 2H \rightarrow Ar.NH.CH_3 + HCl$$

(3) Reduction of the bisulphite addition-products of the anhydroformaldehyde-amines:

$$Ar.NH.CH_2.SO_3Na + 2H \rightarrow Ar.NH.CH_3 + NaHSO_3$$

(4) Hydrolysis of the hydrocyanic acid addition-products of the anhydroformaldehyde-amines, and elimination of carbon dioxide by heat:

$$Ar.NH.CH_2.CN \rightarrow Ar.NH.CH_2.COOH \rightarrow Ar.NH.CH_3 + CO_2.$$

[54] D. R. P. 260234. Harger, *J. A. C. S.*, 41, 270 (1919).

[55] D. R. P. 205415.

A brief discussion of methods hitherto applied for reactions such as the foregoing will be given first, and will be followed by a description of experiments on the methylation of p-aminophenol by these methods. This reaction was chosen because it appears that the indicated methylation has not been effected by the above methods (except the last), and because the product, N-methyl-p-aminophenol, is a compound of considerable interest, its sulphate being the photographic developer known as "Metol."

(*1*) *Hydrogenation of the Anhydroformaldehyde-bases, i. e., of the Group –N:CH–*

The methods by which this reduction has been accomplished include the following:

(a) Reduction by Sodium-amalgam, or by Sodium, and Absolute Alcohol—

These two methods constitute classic means for effecting this hydrogenation.[56] Fischer, avoiding the use of acids because of their decomposing effect upon the –N:CH– group, used the above agents for reductions such as that of benzylidene-aniline to benzylaniline. As is well known, the intensity of the reduction may be modified by use of different alcohols.[57] Attempts to reduce the compound $HO.C_6H_4.N:CH_2$ by these means met with no success.

(b) Reduction by Means of Zinc-dust and Alkali—

This method is the subject of several patents, dealing with the production of secondary from primary amines.[58] The alkylation or arylation is best carried out by interaction of amine and aldehyde in presence of excess of reducing agent; the medium for the reaction is water, alcohol (or acetic acid, but not strong acids.)[59] These methods do not seem to have come into general use, and are probably not highly efficient: several attempted methylations of aniline gave only small yields of methylaniline.

The reduction of benzylidine-p-aminophenol by means of zinc-

[56] O. Fischer, *Ber.*, 19, 748 (1886); *Annal.*, 241, 328 (1887); 245, 279 (1888); Miller and Plöchl, *Ber.*, 25, 2020 (1892).

[57] See, e. g., Miller and Plöchl, *l. c.*

[58] D. R. P. 75854, 105345; Prudhomme, *Bull. soc. chim.*, 23, 69 (1905),

[59] E. P. 102834, A. P. 1221077; *J. C. S.*, 115, 198.

dust and sodium hydroxide, on the other hand, takes place without difficulty,[60] giving good yields of benzyl-p-aminophenol. In view of this fact, it is interesting to record that methylene-p-aminophenol resisted all efforts at reduction by the same process.

(c) Reduction by Zinc in Acid Medium—

Miller and Plöchl[61] showed that anhydroformaldehyde-aniline can be reduced to methylaniline by hydrochloric acid and zinc-dust. Goldschmidt[62] carried out the same reduction with tin and hydrochloric acid. No yields are stated for these reductions.

By reduction of methylene-p-aminophenol with zinc-dust and acid, a partial conversion to N-methyl-p-aminophenol was obtained, as will appear in the experimental part (section III).

(d) Reduction Electrolytically in Alkaline Medium—

By this method Brand and Hönig[63] obtained benzylmethylamine and benzyl-p-aminophenol by the normal course of the reduction, and o-aminophenol and toluene from benzal-o-aminophenol. The writer was able to reduce benzylidine-p-aminophenol in this way, but methylene-p-aminophenol was not hydrogenated.

(e) Reduction Electrolytically in Acid Solution—

Reduction under these conditions suffers the disadvantage that the operation of necessity extends over a considerable period of time, during which certain changes incident to the contact of the condensation-product and acid are in progress. It is therefore thought necessary to maintain a low temperature so long as acid and condensation-product are in contact. According to a recommended procedure,[64] the condensation-product is dissolved in 50 per cent sulphuric acid at −12,° and electrolysis is conducted at or below 0°, using a cathode of lead, copper, nickel, or mercury. In this way both aliphatic and aromatic amines may be alkylated or arylated.

Numerous reductions of methylene-p-aminophenol by a similar process were carried out, using generally 40 per cent sul-

[60] D. R. P. 211869,
[61] *l. c.*
[62] *Chem. Ztg.*, 28, 1229 (1904).
[63] *Zeit. electroch.*, 18, 745.
[64] D. R. P. 143197.

phuric acid and a cathode of lead. Certain of the trials were partially successful, while others, intended to be identical, were attended, so far as could be observed, and for reasons which were not discovered, by no absorption of hydrogen, and by the formation of no detectable secondary amine. The process showed no uniform improvement when conducted at low temperature.

(f) Electrolytic Reduction of Nitro-compounds in Presence of Formaldehyde—

Löb[65] and Goecke[66] carried out reductions of nitrotoluene in hydrochloric acid-alcohol solution, with a lead cathode, and in presence of an excess of formaldehyde. From p-nitrotoluene there were obtained dimethyl-p-totuidine (about 40 per cent), and another compound, called by Löb dimethylditoluidine, and by Goecke trimethylenetritoluidine (but which, it would appear, was probably an anhydroaminobenzyl alcohol).

This process was applied to p-nitrophenol, both in presence of one equivalent of formaldehyde, and of an excess. In neither case could any mono-methyl-derivative be isolated, though some dimethyl-p-aminophenol was obtained; under the first-mentioned conditions some p-aminophenol resulted by simple reduction of p-nitrophenol. Similar reduction of p-nitrosophenol in presence of formaldehyde likewise failed to produce secondary amine.

(g) Reduction by Sodium Hydrosulphite—

The applicability of sodium hydrosulphite for reduction of methylene-amines might appear *a priori* improbable in view of the readiness with which these compounds unite by addition with sulphurous acid or bisulphites; as commercial sodium hydrosulphite always reeks with sulphur dioxide, the immediate formation of the addition-product $Ar.NH.CH_2.SO_3H$ seems probable. Reduction of such compounds to $Ar.NH.CH_3$ by hydrosulphite could hardly be expected.

Attempted reductions of methylene-p-aminophenol by means of sodium hydrosulphite yielded no secondary amine, but a readily soluble yellow-white crystalline substance which evolved sulphur dioxide when warmed with acids.

[65] *Zeit. electroch.*, 4, 428 (1897/8).
[66] Ib., 9, 470 (1903).

(2) *Reduction of the Exochlormethylanilines, formed by Acid Condensation—*

Only a single intance has been found in which such a reduction is reported. Goldschmidt[67] reduced N-methyleneaniline (anhydroformaniline) with tin and hydrochloric acid, condensed the resulting methylaniline with formaldehyde, and then reduced the resulting $C_6H_5.N<^{CH_3}_{CH_2Cl}$ with tin and hydrochloric acid, obtaining dimethylaniline.

A prolonged attempt to duplicate the second reduction, using tin and hydrochloric acid at 100,° was without effect upon the exochlor-compound. Similar experiments were carried out with p-amino-phenol, which was condensed with formaldehyde in presence of hydrochloric or sulphuric acid in varying amounts. The product was subjected to reduction by various means, but in no case could the presence of secondary amine be detected.

(3) *Reduction of the Bisulphite Addition-products of the Anhydroformaldehyde-bases—*

As a means for testing the possibility of effecting the change $Ar.NH.CH_2.SO_3H \rightarrow Ar.NH.CH_3 + HSO_3Na$, the bisulphite addition-product of methyleneaniline was prepared from formaldehyde-bisulphite and aniline,[68] and was reduced by tin or zinc and hydrochloric acid. In both cases free sulphur was separated, but steam-distillation of the alkalized liquid yielded no volatile product. The possibility of splitting off the $-SO_3H$ group hydrolytically was also studied, but positive results were not obtained.

(4) *Hydrolysis of the Hydrocyanic Acid Addition-products of the Anhydroformaldehyde-Bases, and Elimination of Carbon Dioxide by Heat—*

The decarboxylation of p-hydroxy-phenyglycine was suggested by Paul[69] as a method for preparation of methyl-p-aminophenol. Trial of this method by Harger[70] gave poor results, and led him to a further study of the method of Merck and Co., using hydro-

[67] *Chem. Ztg.*, 28, 1229 (1904).
[68] Orloff, *l. c.*, p. 37.
[69] *Zeit. angew. Ch.* 10, 17 (1897).
[70] *J. A. C. S.*, 41, 270 (1919).

quinone and methylamine.[71] The writer made no trial of Paul's method.

III. Experimental Results on the Methylation of p-Aminophenol by Means of Formaldehyde.

Results by methods (2) and (3) (see page 14) will be given briefly first. Method (4) was not subjected to trial, and need not be referred to again. Method (1), on which numerous experiments were made, will be considered last.

Reduction of Exochlormethyl-p-aminophenol,

$$HO.C_6H_4.NH.CH_2Cl—$$

According to the general reaction given on page 12 (d), p-aminophenol would react with formaldehyde in hydrochloric acid solution as follows:

$$HO.C_6H_4.NH\boxed{H.\ H}Cl + \boxed{O}CH_2 \rightarrow HO.C_6H_4.NH.CH_2Cl + H_2O.$$

(exochlormethyl-p-aminophenol)

The condensation-product loses hydrochloric acid under the influence of alkali (sodium carbonate), and is converted into hydroxy-anhydro-aminobenzylalcohol, $HO.C_6H_3<\begin{matrix}NH\\|\\CH_2\end{matrix}$, which is insoluble in water. The instability of the exochlor-compound in presence of alkali must be borne in mind in selecting a method for its reduction. Alkaline reduction is excluded, as the anhydrobenzylalcohol-derivative would form at once, and on reduction would yield an oxytoluidine.[72] Acid reduction, after the anhydroaminobenzylalcohol is once formed, is also inadmissible, as this compound, when dissolved in dilute acids, does not revert to the exochlor-compound, but, by virtue of its character as a secondary amine, forms a salt.

For the preparation of exochlormethyl-p-aminophenol, recourse was had to the method of Goldschmidt,[73] and to several patented

[71] D. R. P. 260234; A. P. 1297685 (Harger).

[72] D. R. P. 83544.

[73] *Chem. Ztg.*, 24, 284 (1900).

processes.[74] The last-mentioned patent deals with the condensation of formaldehyde with para-substituted aromatic bases (not p-aminophenol), and seems therefore to be especially relevant, though it is the alkali transformation-products of the exochlor-compounds the preparation of which is there described. The exochlor-compounds formed remain for the most part in solution. This is the case also when the simple primary aromatic amines are condensed with formaldehyde in dilute acid solution, but contrasts with the behavior of the secondary amines, the exochlormethyl-derivatives of which are precipitated by hydrochloric acid, though soluble in water.[75]

Isolation of the compound $HO.C_6H_4.NH.CH_2Cl$, obtained from $HO.C_6H_4.NH_2.HCl$ and formaldehyde, was undertaken in a number of experiments, in which the acidity ranged from that of the p-amino-phenol hydrochloride itself to that produced by addition of about an equal volume of concentrated hydrochloric acid to the solution. Sulphuric and acetic acids also were used. The solid product of such condensations was in general scanty, dark brown in color, and amorphous; it frequently separated in coherent and glue-like masses. Only at the higher concentrations of acid was there a reasonably copious separation of solid material. Thus, using 20 grams of p-aminophenol hydrochloride in 90 cc. of water, 25 grams of 38 per cent formaldehyde (more than two equivalents), and 95 cc. of concentrated hydrochloric acid, and allowing condensation to proceed in the cold overnight, only a small amount of material separated. After heating for some time on the water-bath, a dark brown powder and some lumps separated on chilling. When dried, this material weighed 14 grams, a yield of 64 per cent, assuming it to be the compound $HO.C_6H_4.NH.CH_2Cl$. It was found to be soluble in hot water, from which it separated in muddy form on chilling, though with considerable loss. The aqueous solution was precipitated by the common acids; sodium carbonate solution produced a flocculent precipitate; the material dissolved very readily in caustic soda. The "recrystallized" material dried to a rather brittle, resinous

[74] D. R. P. 96851, 97710, 122474.

[75] Goldschmidt, *Chem. Ztg. l. c.*; *Ib.*, 26, 606 (1902); D. R. P. 97710.

mass, yielding when ground a chocolate-brown powder. It responded positively for chlorine both to the copper-wire test, and to silver nitrate in water solution. The latter may be taken as an indication of impurity.[76] The same conclusion was reached by analysis for nitrogen (Kjeldahl), 7.9 per cent being found, instead of 8.9 per cent as required by the formula. When condensation was carried out in larger volumes, and with less acid present, practically no precipitate appeared. In all these condensations the liquid became deep red in color.

Reduction of such solutions with zinc-dust, or with tin,[77] by sodium amalgam (keeping the solution slightly acid), by sodium hydrosulphite, or by electrolysis in sulphuric acid solution, yielded no secondary amine separable as nitrosamine. Similar results were obtained using the isolated condensation-product.

Reduction of the Bisulphite Addition-product of Methylene-p-aminophenol—

The additive union of sulphurous acid and its salts with formaldehyde condensation-products of the aromatic amines was studied by Eibner.[78] The formation of the compound $HO.C_6H_4.NH.CH_2.SO_3Na$, or $(HO.C_6H_4.N:CH_2)NaHSO_3$, is the subject of D. R. P. 68707: p-aminophenol is condensed with formaldehyde in alkaline solution, the product is precipitated by carbon dioxide, dissolved promptly in sodium bisulphite solution, and the addition-product obtained by crystallization. The bisulphite compound is very soluble in water, and crystallizes as small nearly white plates. This compound can be very conveniently prepared by addition of solid p-aminophenol to a hot concentrated solution of formaldehyde bisulphite. The base passes into solution; when chilled, the liquid sets to a mass of crystals. A fairly strong solution of this product, when acidified with sulphuric or hydrochloric acid, separated small glistening crystals, much less soluble in water than the original compound, but readily soluble in alkali. Hot dilute sulphuric acid liberated sulphur dioxide; the odor of formaldehyde was noticed also. It seems

[76] D. R. P. 96851.

[77] Goldschmidt, *Chem. Ztg.* 28, 1229 (1904).

[78] *Annal.*, 316, 89 (1901).

that this compound is the free acid $HO.C_6H_4.NH.CH_2.SO_3H$. Eibner[79] reported an analogous behavior of the corresponding aniline compound.

Efforts to convert the compound $HO.C_6H_4.NH.CH_2.SO_3Na$ into $HO.C_6H_4.NH.CH_3$ were referred to on page 18.

Hydrogenation of N-Methylene-p-aminophenol, $(HO.C_6H_4.N:CH_2)_n$

Experiments included under the above heading constitute the chief experimental basis of this paper, and will be described with more detail than was thought desirable for other methods. The principal operations in all of the methods to be described are

(1) Condensation of p-aminophenol and formaldehyde in alkaline solution.

(2) Reduction of the condensation-product.

(3) Isolation of the methylated base

(1) *Condensation of p-Aminophenol and Formaldehyde in Alkaline Solution—*

According to the directions of D. R. P. 68707, p-aminophenol is dissolved in water (21 grams per liter), the solution filtered, chilled to 5°—10,° and treated with somewhat more than one equivalent each of sodium hydroxide and formaldehyde. The solution is allowed to stand several hours, and the condensation-product, present in solution as the phenolate, is precipitated by conducting carbon dioxide into the liquid, or by addition of soda. The liquid always possesses a strong and offensive "fishy" odor, and darkens promptly when exposed to air. The precipitated methylene-base is generally flocculent, and light in color, with often a pinkish cast. If incorrectly precipitated, it may appear in the form of large coherent lumps.

The condensation-product is insoluble in water, ether, or benzene; it is soluble in alcohol, readily soluble in alkali, the solution thus obtained having the properties, as regards odor and air-oxidation, of the original condensation-liquid; the alkaline solution reduces silver salts. The condensation-product is precipitated from alkaline solution by addition of acids, but the

[79] *l. c.*

precipitate dissolves in a sufficient excess of the acid: the odor of formaldehyde can then be detected, indicating hydrolysis of the methylene-base. When dried in air, methylene-p-aminophenol darkens somewhat, as a result of polymerization, and probably of oxidation.

It was found convenient to use p-aminophenol hydrochloride instead of the free base, because of the greater stability and solubility of the former. Most of the material used was the Eastman product. It contained 1.39 per cent of inorganic material (ash), and 0.12 per cent moisture. Early experiments were made using Kahlbaum's p-amino-phenol hydrochloride, and some others using material prepared electrolytically by Dr. H. S. Lukens.

For the purification of p-aminophenol hydrochloride advantage was taken of the fact that this salt is precipitated almost completely when its strong solution, externally cooled, is saturated with gaseous hydrochloric acid. To obtain the free base for immediate use, a concentrated solution of the hydrochloride, cooled to about 0°, was treated with strong sodium carbonate solution until effervescence ceased. The base separated in granular form, and was filtered off and pressed. The yield by this method is good, the solubility of the base at 0° being about 1 part per 100 of water. The product contains alkali, and cannot be dried or kept. To prepare p-aminophenol in stable form, it is advisable to crystallize it from hot water containing bisulphite, and to wash it with cold bisulphite solution.

To study the condensation quantitatively, the methylene-base, after formation under the selected conditions, was precipitated from the properly diluted solution, washed with water, dried carefully, and weighed. The procedure for the isolation is given later. In some of the later experiments the uncondensed p-aminophenol was precipitated from the filtrate in the form of its benzylidine-derivative. The latter is precipitated[80] by shaking the solution, acidified with acetic acid, with benzaldehyde. The product is washed with water, dried, and weighed.

The results obtained under various conditions of condensation appear in Table I.

[80] Haegele, *Ber.*, 25, 2753 (1892); *Cf.* Michaelis, *Ber.*, 27, 3005 (1894)

TABLE I.

Note: "P. A. P."=p-Aminophenol hydrochloride.

P. A. P. gms.	CH_2O 38% gms.	NaOH gms.	Vol. cc.	Time hrs.	Method of precipitation	Nature of product	Dry cond. prod.	% Yield	Benzal-comp. from filt.	% P. A. P. not cond.	Total P. A. P. acctd. for
10	5.6 theory	7.5	100	2.5	$NaHCO_3$ sol.	Finely granular	6.5	78			
10	6.0	7.5		2.5	" "	" "	6.6	79			
10	6.0	7.5	to	2.5	" "	" "	6.6	79			
10	11.2 excess	7.5		2.5	" "	" "	6.7	80			
10	6.0	15 excess		2	" "	" "	6.5	78			
10	6.0	7.5	200 in ice	2	" "	Large lump	7.0	84			
10	6.0	7.5	" in ice	2	Carbon dioxide	Granular	7.0	84			
10	6.0	7.5	" in ice	2	30% CH_3COOH added rapidly	Resinous	5.0	60			
10	6.0	7.5	" in ice		30% CH_3COOH added slowly	Finely granular	7.1	85			
10	6.0	7.5	250	4	" " "	" "	7.0	84			
10	6.0	7.5	200	2	" " "	" "	5.6	67	4.0	29	96
10	6.0	7.5	60	2	" " "	" "	6.4	77	2.8	21	98
10	6.0	7.5	1000	2	" " "	" "	6.0	72	4.7	34	106
5	3.0	3.8	50	2	" " "	" "	3.2	77	1.4	21	98

The data just given seem to justify the following conclusions:

(1) The extent of the condensation is relatively independent of experimental conditions, provided that there are present at least one equivalent of formaldehyde, and two equivalents of sodium hydroxide, for each equivalent of p-aminophenol hydrochloride (or one equivalent of sodium hydroxide if free p-aminophenol is used). Excess of formaldehyde or of sodium hydroxide is without apparent effect.

(2) Low temperature favors slightly increased condensation, as shown by the sixth, seventh, and ninth experiments, in comparison with other trials, which were conducted at 15°—20.°

(3) Condensation is not increased by prolongation of the time beyond two hours. As shown by experiments not listed above, over-night condensations tend to yield a denser and darker product, with no advantage in the matter of yield or of ease of reduction.

(4) The volume in which condensation occurs is almost without effect. The only definite exception to this statement is presented by the thirteenth experiment, in which the volume was relatively large, the result being that normal condensation was not quite complete at the end of two hours.

(5) The last four experiments indicate that practically all the p-aminophenol hydrochloride taken initially is accounted for, either as methylene-p-aminophenol or as the uncondensed base.

(6) Condensation of formaldehyde and p-aminophenol occurs to the extent of about 75 to 85 per cent.

The experiments recorded above, together with many incidental observations made during the course of the work, led to the adoption of the following

Procedure for Condensation of Formaldehyde and p-Aminophenol—

(a) Condensation—Dissolve 10 parts of p-aminophenol hydrochloride in about 60 parts of water, and filter the solution. Transfer the filtrate to a flask, and chill well under the tap, or better in ice. Add at one time one-half of a solution which contains 7.5 parts (somewhat more than two equivalents) of sodium

hydroxide, and cool until the heat of neutralization is absorbed. Now add the remaining sodium hydroxide, which will dissolve the precipitated p-aminophenol. To the cold alkaline solution add 6 parts of 38 per cent formaldehyde (somewhat more than one equivalent) gradually, with rotation of the flask. Insert a stopper, and keep the flask in a cool place for two or three hours.

(b) Isolation—Pour the liquid into a large beaker or jar containing cold water, and provided with an efficient mechanical stirrer, and, appropriately supported above the precipitating vessel, a separatory funnel containing 30 per cent acetic acid. The volume at the time of precipitation should be rather large, or the liquid will become so filled with the precipitated product as to interfere with effective stirring. A volume somewhat greater than 500 cc. is convenient for precipitation of the condensation-product from 10-15 grams of p-aminophenol hydrochloride. With the stirrer in motion, allow 30 per cent acetic acid to drop into the liquid, until the reaction is distinctly acid to litmus. The condensation-product will be precipitated in a finely granular form which settles promptly and is easily filtered and washed. Filter off the product on a Büchner funnel, wash with cold water, press down well with a spatula, and dry the material as far as possible by suction. Transfer it to a watch-glass or plate, and keep in a *slightly* warm place for several hours, with occasional reduction of lumps as drying progresses. Dry finally at 80°-90.° The product is thus obtained as a loose, soft, grayish powder, which assumes a brown color after long exposure to the air. If the drying is done too rapidly, the condensation-product may become resinous.

Precipitation by carbon dioxide gives equally good results, but is less rapid and less convenient; the use of sodium bicarbonate solution for the precipitation occasionally caused the separation of a coherent product.

When reduction of the methylene-p-aminophenol is intended, it should be used shortly after precipitation, and without drying, as the completely dried product is reduced with difficulty. As will appear below, isolation of the condensation-product is not essential, and is quite properly omitted.

Before the reduction of methylene-p-aminophenol is discussed, it is necessary to describe the methods of forming and handling the nitrosamine of N-methyl-p-aminophenol, since it is in this form that the reduction-product can be most readily and completely isolated, and the effectiveness of the reduction determined.

p-Hydroxy-methylphenylnitrosamine, $HO.C_6H_4.N<^{NO}_{CH_3}$

This compound is obtained by the usual procedure for nitrosamine formation: addition of sodium nitrite solution to the chilled acidified solution of the secondary amine. It separates from solution in crystalline form, the color of the crystals depending upon the presence of impurities in the solution. The pure secondary base yields nearly white, or gray, minute needles, having a low solubility in cold water. When precipitation is effected from solution containing p-aminophenol, formation of the nitrosamine is noticeably delayed, due no doubt to the superior reactivity of the primary base. In such cases, also, tar-formation is almost invariable, and the nitrosamine separates as brown granular crystals. Under unfavorable conditions the separation of tar has been considerable, rendering purification of the nitrosamine, without considerable loss, impossible.

The nitrosamine is a somewhat unstable compound, and suffers serious decomposition, with darkening, if an attempt is made to dry it while moist with any trace of the acid mother-liquor, or to crystallize it from strong alcohol; less extensive decomposition occurs if dilute alcohol is used. Rather oddly, the compound seems to be most satisfactorily crystallized from hot water, in which it is moderately soluble. For this purpose, the nitrosamine is suspended in water (about 50 cc. for each 3 grams), the mixture heated nearly to boiling, and about 5 cc. of alcohol added. Solution is completed without unnecessary heating, and the liquid is cooled in ice. The nitrosamine crystallizes out rapidly, and with nearly quantitative completeness.

For purposes of comparison, 2.0 grams of Metol (Hauff) were dissolved in 200 cc. of water, 10 cc. of strong hydrochloric acid added, and the solution cooled in an ice-bath. It was then treated dropwise with a 20 per cent solution of sodium nitrite,

until a drop of the liquid, applied to potassium iodide paper, showed presence of nitrous acid in excess. The nitrosamine separated, during the addition of nitrite, as minute almost white needles, which were filtered off, and washed sparingly with cold water. After several recrystallizations from dilute alcohol, the nitrosamine was obtained as fairly large flat needles, slightly straw-tinged, and melting at 134.3° (corr.), with decomposition above the melting temperature. In regard to the melting-point of the nitrosamine, it should be added that Clarke[81] gives 136°, a value never obtained by the writer.

An interesting behavior was observed when an excess of nitrous acid was allowed to act upon the precipitated nitrosamine. There was obtained a bright yellow insoluble powder, which melted with decomposition at 126°-127°, with previous softening. The bottle in which this material was kept was gradually colored a bright red on its entire inner surface. The reaction recalls the simultaneous nitrosation and nitration of methylaniline by means of nitrogen dioxide, as described by Stoermer.[82]

Finally, it is of interest to consider the formation of the nitrosamine as an identification test for N-methyl-p-aminophenol. Attention may be called to the mercuric acetate test described by Harger[83] which is said to disclose the presence of metol in a concentration of 1:100000 by the gradual development of a grape-juice color. The nitrosamine test is by no means so delicate as this, but is more characteristic. It appears that the mercuric acetate test is not entirely specific, since a by-product was obtained, by ether extraction of the alkalized solution after reduction of methylene-p-aminophenol, which was obviously not methyl-p-aminophenol (its sulphate was excessively soluble in water), but which responded to the mercuric acetate test more strongly than "metol" itself. The color developed was nearly blue, but in cases of doubt would certainly cause confusion.

To test a material for presence of a salt of methyl-p-aminophenol, a little of the substance is dissolved in a small volume of

[81] *J. Ind. Eng. Chem.*, 10, 891 (1918).
[82] *Ber.*, 31, 2523 (1898).
[83] *J. A. C. S.*, 41, 270 (1919).

water, the solution acidified with a drop or two of hydrochloric acid, chilled, and sodium nitrite solution added in slight excess. A precipitate of minute needles, which usually appears suddenly, and which seems to fill the liquid, constitutes a positive test. If this material is recrystallized from a little water containing alcohol, and its melting-point determined, the identification of methyl-p-aminophenol may be regarded as certain. Identification by means of the sulphate or the dibenzoyl-compound is less convenient, as these derivatives are less characteristic in appearance, and have higher melting-points.

(2) *Reduction of N-Methylene-p-aminophenol to N-Methyl-p-aminophenol-*

Reference to page 15 shows the investigated methods of reduction to be the following:

(a) Reduction by Sodium Amalgam, or Metallic Sodium, and Alcohol.

(b) Reduction by Zinc-dust and Alkali.

(c) Reduction by Zinc-dust and Acid.

(d) Reduction Electrolytically in Alkaline Solution.

(e) Reduction Electrolytically in Acid Solution.

(f) Reduction Electrolytically of p-Nitrol-phenol or p-Nitroso-phenol in presence of Formaldehyde.

(g) Reduction by Hydrosulphite.

In all cases the success of the reduction was tested by means of the nitrosamine reaction. Of the above methods, only method (c) yielded positive results which were uniformly reproducible. Method (e) was attended with some success, and would possibly repay closer study. The other methods were apparently quite unsuccessful, and may be disposed of rather briefly.

(a) Reduction by Sodium Amalgam, or by Sodium, and Absolute Alcohol— Both aqueous (acid or alkaline) solutions of the condensation-product, and alcoholic solutions, were subjected to action of sodium amalgam. Reduction by metallic sodium was applied to the solution of methlyene-p-aminophenol in anhydrous ethyl alcohol. In neither case could

presence of secondary amine be detected in the liquids, after suitable preparation for precipitation of nitrosamine.

(b) Reduction by Zinc-dust and Sodium Hydroxide—

This method was applied to the reduction of benzylidene-p- aminophenol and of methylene-p-aminophenol, obtained from p-aminophenol by condensation with, respectively, benzaldehyde and formaldehyde. It was expected that these compounds would behave similarly upon reduction; their chemical similarity is shown by the formulas $HO.C_6H_4.N:CH.C_6H_5$ and $HO.C_6H_4.N:CH_2$.

Reduction of benzylidine-p-aminophenol[84] was quite successful: 17 grams of this compound gave 18 grams of benzyl-p-aminophenol hydrochloride, a yield of 89 per cent. The base was found to melt at 87°-88°; the nitrosamine, crystallized from dilute alcohol, melted at 142.5° (corr.). A picrate was prepared, as large bright yellow irregular prisms, very sparingly soluble in water, and melted at 166°-167° (corr.). It should be noted that the melting-point of the nitrosamine is given[85] as 148°.

The same procedure, as well as that of A. P. 1221077, with varying temperatures, concentrations of alkali, and proportions of base and formaldehyde, when applied to the reduction of methylene-p-aminophenol, failed to produce any methyl-p-aminophenol which could be separated as nitrosamine.

(c) Reduction by Zinc-dust and Acid—This method will be discussed in some detail below.

(d) Reduction Electrolytically in Alkaline Medium—

As a test of the method, the benzylidine-p-aminophenol obtained from 22 grams of p-aminophenol hydrochloride and 16 grams of benzaldehyde was dissolved in 12 per cent sodium hydroxide solution, and subjected to reduction using iron electrodes. Absorption of hydrogen was very imperfect. A current of about 5 amperes (cathode area about 220 cm.^{2} was continued for 3.5 hours, with continuous evolution of unabsorbed hydrogen. The liquid was finally acidified with sulphuric acid, filtered, and

[84] D. R. P. 211869.

[85] *Zeit. electroch.*, 18, 745.

chilled, when 2 grams of the difficulty soluble benzyl-p-aminophenol sulphate separated. The nitrosamine of this product melted at 142° (see page 30).

The same procedure was applied for the reduction of methylene-p-aminophenol dissolved in 15 per cent sodium hydroxide solution. There was no apparent absorption of hydrogen, and no methylated product was detected in the liquid after reduction.

(e) Reduction Electrolytically in Acid Solution—

The electrolytic cells used in all reductions recorded in this paper were identical in design with the cell devised by Dr. H. S. Lukens, whose description of it is now awaiting publication. Cells of three sizes were used, having capacities of 500 cc., 250 cc., and 100 cc. The last mentioned was used for reductions at lower temperatures. The porous cup of this cell was closed by a large rubber stopper[86] which served as a support for the lead electrode, the liquid seal of the stirrer, the vent-tube, and an in-

TABLE II.

Electrolytic Reductions

P. A. P. gms.	Method of preparation for electrolysis	Amp.	Volt	Temp.	Time hrs.	Gas	Nitrosamine gms.	% Yield
12.5	Condensed overnight. Poured into equal vol. 40% H_2SO_4	10	4	—	6	None at first	1.0	8
25	Condensed 36 hours. Added to equal vol. 80% H_2SO_4	5.5-7	4	—	3	+ after 1 hr.	+	
12.5	Condensed 2 hours. Ppted, by CH_3COOH; dissolved in 45 gms. 25% H_2SO_4, added 40 cc. 80% H_2SO_4. Small cell	2	3.5	3°-4°	3.5	+ from start	0.2	1.6
12.5	Condensed overnight; ppted. by CO_2; dissolved in 90 cc. 40% H_2SO_4 at 5°. Small cell	2	4	5°-9°	5	+ after 1 hr.	2.4	18
12.5	Condensed 2 hours; ppted. by CH_3COOH; dissolved in 200 cc. 20% alcoholic H_2SO_4	10-11	6-7	not cooled	4	Little for 1 hr., then +	1.0	8

[86] Tafel, *Ber.*, 33, 2209 (1900.)

serted thermometer. The electrodes of these cells were made of commercial lead.

Results of some of the electrolytic reductions are tabulated above. The temperature, during addition of acid to condensation-product (either isolated or in solution) was kept low[87] so as to avoid hydrolysis of the condensation-product.

A number of experiments not listed above were entirely without positive result. The effect of amalgamating the cathode, or of using very pure lead, was not investigated. In the last experiment, an aliquot portion was examined, after reduction, for unchanged p-aminophenol: 37.5 per cent of that initially taken was recovered.

(f) Electrolytic Reduction of p-Nitrophenol or of p-Nitrosophenol in Presence of Formaldehyde—

Reference may be made to the statements which appear under the same heading on page 17.

The reduction of 15 grams of p-nitrophenol in alcohol-hydrochloric acid solution, in presence of 10 grams of 38 per cent formaldehyde (about one equivalent), absorbed the hydrogen from a current of 10 amperes for over an hour. Electrolysis was continued for nearly five hours, when evolution of unabsorbed gas was rapid. The clear red liquid was distilled free from alcohol, made alkaline with sodium carbonate, filtered, and extracted with ether. During distillation of the ether, a quantity of small crystalline plates separated. These were removed (1.4 gram), and were identified as p-aminophenol [m. p., 183°-185°; m. p. of benzylidine-derivative, 185°]. The solid material precipitated by sodium carbonate was dissolved in dilute hydrochloric acid, boiled with charcoal, filtered, and the solution precipitated by sodium acetate. A white amorphous material, weighing 2.2 grams, was obtained. This product seems to correspond to the by-product obtained by Löb and by Goecke during the electrolytic reduction of p-nitrotoluene in presence of formaldehyde, and is possibly an anhydroamino-oxy-benzyl alcohol.

The oil left after evaporation of the ether was subjected to vacuum distillation. At 18 mm., distillation began at 162°, and

[87] D. R. P. 143197.

was continued up to 175° (25 mm.). The product was a dark brown, viscous oil, which could not be solidified; its amount was too small to warrant purification. The data from the distillation furnish some basis for the belief that dimethyl-p-aminophenol (b. $p._{80} = 162°$) was present.

A number of similar reductions of p-nitro-phenol and of p-nitrosophenol were carried out in presence of formaldehyde, but in no case could any secondary base be isolated after reduction. This method seems to serve only for the formation of dimethylanilines from the corresponding nitro- or nitroso-compounds; mono-methylation apparently does not occur.

(g) Reduction by Sodium Hydrosulphite—
No addition need be made to the remark on page 17.

(c) Reduction of N-Methylene-p-aminophenol to N-Methyl-p-aminophenol by Zinc-dust and Acid-

After a number of preliminary trials, evidence of methylation, by zinc-dust and dilute hydrochloric acid, was first obtained by isolation of a benzoyl-compound melting at 172°-177° (m. p. dibenzoyl-methyl-p-aminophenol = 174°). By a similar procedure, using sulphuric acid, a nitrosamine melting at 133°-134° was obtained, identical with that from metol. It was found that reduction by zinc and acid could be effected either with or without isolation of the condensation- product $HO.C_6H_4.N:CH_2$. The yields were always small, however, a fact at first attributed to the decomposition of the methylene-p-aminophenol by hydrolysis. Data to be given later will show that this hydrolysis is by no means so considerable as was thought.

The conditions by variation of which the reduction might be expected to be influenced are rather numerous; experiment has shown, however, that the process is actually rather unresponsive to modifications in conditions. The opinion is held at present that the small extent of the methylation is due in large part to a side-reaction of the same kind as that which diminished to about 40 per cent the yields in Löb's and in Goecke's electrolytic reductions referred to previously. There seems to be reason to be-

lieve that this side-reaction is only the normal action of acid upon the formaldehyde condensation-product, as shown on page 8.

Results of a number of experiments will now be tabulated, showing the influence of various conditions upon the reduction. It is to be emphasized that the yields set down in Tables III, IV, and V, neglect the recoverable p-aminophenol present after reduction, and are calculated on the basis of total p-aminophenol taken initially and that finally obtained in the methylated form (as nitrosamine). These yields are therefore given too low by about 10 per cent.

TABLE III.

Experiments to determine

(a) Relative values of several methods for precipitating condensation-product.

(b) Necessity for isolation of condensation-product.

P. A. P. gms.	Preparation for reduction	Temp. of reduc. tion.	Nitrosamine gms.	% Yield	Remarks
12.5	Condensed over-night. Ppted. by CO_2; dissolved in 40% H_2SO_4 at 5°.	in ice	3.5	27	Precipitation by CO_2
10	Condensed 2 hrs. Ppted. by CO_2; dissolved in 40% H_2SO_4 at 1°.	5°–8°	2.2	21	
10	Ppted. by CO_2; diss. 40% H_2SO_4 at -2°.	-2 to +8°	2.2	21	
12.5	Ppted. CH_3COOH; diss. 50% H_2SO_4 (ice)	in ice	2.9	22	Pptation. by CH_3COOH
10	Ppted. CH_3COOH; diss. 40% H_2SO_4, -2°.	-2 to +8°	2.1	20	
20	Ppted. $NaHCO_3$ (large lump); diss. in 40% H_2SO_4 at 0°.	c-6°	4.0	19	$NaHCO_3$
10	Not isolated; sol. added to equal vol. (190 cc.) 40% H_2SO_4 at 15°.	15°–33°	2.2	21	Not isolated; not cooled.
10	Not isolated; sol. added to equal vol. (130 cc.) 40% H_2SO_4 at 17°.	17°–37°	2.7	26	

The data in Table III indicate that

(a) The condensation-product may be precipitated equally well by carbon dioxide or acetic acid, but less advantageously by sodium bicarbonate.

(b) No advantage is gained by isolation of the condensation-product. It is indicated also that low temperatures are not essential (see Tables IV and V).

TABLE IV.

Experiments to determine

(a) Effect of variation in concentration of acid.

(b) Effect of variation in volume in which reduction occurs.

(c) Necessity for cooling before and during reduction.

P. A. P. gms.	Preparation for Reduction	Temp. of Reduction	Nitrosamine gms.	% Yield	Remarks
10	Pptd. by CH_3COOH; dissolved in 25% H_2SO_4 at 4°	low	1.8	17	25% H_2SO_4
10	Pptd. by CH_3COOH; dissolved in 40% H_2SO_4 at -2°	-2° to + 8°	2.1	20	40% H_2SO_4
10	Pptd. by CH_3COOH; dissolved in 50% H_2SO_4 at 4°	low	1.9	18	50% H_2SO_4
10	Pptd. by CO_2; dissolved in 190 cc. 40% H_2SO_4 at -5°	2°	1.6	15	
10	Pptd. by CH_3COOH; dissolved in 50 cc. 40% H_2SO_4 at -5°	-1°	2.1	20	
10	Pptd. by CH_3COOH; dissolved in 100 cc. 40% H_2SO_4, -8° to -2°	-2° to + 28°	2.2	21	Effect of temp. variations
10	Pptd. by CO_2; dissolved in 40% H_2SO_4 at 5°	0° to + 5°	2.5	24	
10	Not isolated; equal volume (190 cc.) 40% H_2SO_4 added, 15°	15°-33°	2.2	21	
10	Not isolated; equal volume (130 cc.) 40% H_2SO_4 added, 17°	17°-32°	2.7	26	

The above experiments show that

(a) No decided effect is caused by variations in the initial concentration of sulphuric acid.

(b) Somewhat better results are obtained when the volume is restricted (see Table V).

(c) No advantage is gained by working at low temperatures.

In subsequent experiments the condensation-product was not isolated. The condensation liquid was transferred to a beaker, provided with a mechanical stirrer, some zinc-dust was added, and an excess of 40 per cent sulphuric acid was introduced. While stirring actively, zinc-dust was added so as to maintain it in excess. In several experiments, the condensation liquid was added

slowly to an excess of acid and zinc-dust. Results of further experiments are shown in Table V.

TABLE V.

Experiments to determine

(a) Effect of reduction at higher temperatures

(b) Effect of variations of volume in which reduction occurs.

(c) Effect of gradual addition of condensation liquid to sulphuric acid and zinc-dust.

(Reduction of methylene-p-aminophenol without isolation.)

P. A. P. gms.	Preparation for reduction	Temp. of reduction.	Nitrosamine gms.	% Yield	Remarks
10	Added equal volume (70 cc.) of 40% H_2SO_4.	15°–2°	2.2	21	Average temp. 5°
10	Added 125 cc. 40% H_2SO_4 to solution diluted to 400 cc.	25°–40°	3.3	31	" 35°
10	Added equal volume (70 cc.) of 40% H_2SO_4.	50°–28°	3.3	31	" 40°
10	Added equal volume (120 cc.) of 40% H_2SO_4.	30°–86°	3.6	34	" 60°-80°
10	Added equal volume (100 cc.) of 40% H_2SO_4.	70°–90°	3.3	31	" 90°
10	Added equal volume (100 cc.) of 40% H_2SO_4.	65°–103°	3.2	30.5	" 100°
10	Added equal volume (65 cc.) of 40% H_2SO_4.	60°–90°	2.5	24	Reduction in small vol.
10	Solution added dropwise to equal volume (116 cc.) of 40% H_2SO_4 containing zinc-dust: 25 gms. zinc in all.	20°–49°	2.5	24	Condensation liquid added to zinc and H_2SO_4
10	Same as above; volume = 65 cc. Added rapidly to zinc and H_2SO_4.	60°–80°	2.6	25	
10	Same as above; volume = 100 cc. Higher temperature.	80°–90°	3.0	29	

The results in Table V justify the conclusions that

(a) The most favorable reduction temperature is rather high, lying above 50°, and probably at 70° to 80°.

(b) Variations in the volume of the liquid in which reduction is effected do not have any definite effect upon the results. Smaller volumes are preferable for reasons of convenience.

(c) No improvement is caused by gradual addition of the condensation liquid to sulphuric acid in which zinc-dust is kept in excess, to avoid prolonged contact of acid and condensation-product before the latter can be reduced.

Miscellaneous Experiments—

Reduction of Dried Condensation-product—

Eighteen grams of dried methylene-p-aminophenol were dissolved in 150 cc. of 40 per cent sulphuric acid, and reduced with 15 grams of zinc-dust at 0° to 5°. There was obtained 2.2 grams of nitrosamine, corresponding to 11.6 per cent reduction.

In another experiment, methylene-p-aminophenol which had become resinous on drying was similarly treated. In contact with acid, the dark red powder coagulated into a single glue-like mass, which remained unattacked upon addition of zinc-dust.

These experiments demonstrate the increased difficulty in reduction which is consequent upon drying the condensation-product, presumably as a result of polymerization.

Effect of Presence of Excess Formaldehyde added to Condensation-liquid previous to Acidification and Reduction—

For experimental conditions, see last experiment in Table III. After condensation, 10 grams of 38 per cent formaldehyde were added, and then one volume of 40 per cent sulphuric acid. Reduction was carried out as usual. Addition of sodium nitrite caused brisk effervescence, but no nitrosamine was formed.

The prevention of hydrolysis of methylene-p-aminophenol was therefore not achieved, while normal reduction was in some way prevented, by presence of excess formaldehyde in the acid solution.

From the preliminary experiments, the results of which are recorded above, was developed the procedure used in succeeding experiments, in which the course of the reaction was examined somewhat more closely.

The extent to which p-aminophenol escapes condensation with formaldehyde is shown in Table I (page 24). The p-aminophenol

present after reduction includes this, in addition to any formed by acid hydrolysis of the methylene-p-aminophenol.

Recovery of unchanged p-aminophenol from the solution after reduction is readily effected by condensation with benzaldehyde.[88] For this purpose, the solution is nearly neutralized (left slightly acid), sodium acetate is added, and the liquid is shaken with a slight excess of benzaldehyde. The benzylidine p-aminophenol separates as light-colored flocks or clumps, which adhere to the vessel if too large an excess of benzaldehyde is present. The precipitate, when completely formed, is filtered off, and washed with water. It may be dried and weighed, 1.0 gram corresponding to 0.73 gram of p-aminophenol hydrochloride. Benzylidine-p-aminophenol is readily crystallized from dilute alcohol as small pale yellow needles which melt at 185°. It is well adapted to the identification of p-aminophenol.

To recover p-aminophenol and benzaldehyde from benzylidine-p-aminophenol, advantage was taken of the ready hydrolysis of the last-named by strong acids. The product was transferred to a distillation-flask, water added to make a paste, about an equal weight of strong hydrochloric acid added, and the mixture distilled with steam. The benzylidine-p-aminophenol was thus decomposed, and the benzaldehyde formed passed into the distillate. It was extracted therefrom by ether, and recovered by distillation. The acid liquid from the decomposition was treated so as to obtain the p-aminophenol hydrochloride (see page 23). Working in this way, there was obtained, from 37 grams of benzylidine-p-aminophenol,

17.8 grams of benzaldehyde (178°-185°)	90 per cent.
23.2 grams of p-aminophenol hydrochloride	85.6 per cent.

Preparation of N-Methyl-p-aminophenol from its Nitrosamine

Among the methods suggested for replacement of the nitroso-group by hydrogen may be mentioned

[88] D. R. P. 208434.

(a) Reduction by tin, zinc, or iron, and acid.[89] It will be recalled that by milder reduction, hydrazine derivatives are formed.[90]

(b) Action of strong hydrochloric acid, or gaseous HCl.[91]

(c) Heating with aniline.[92]

Several attempts to convert p-oxy-phenylmethylnitrosamine to the secondary base, by action of hydrochloric or sulphuric acid, resulted unsuccessfully. Decomposition occurred readily, with evolution of nitrogen oxides, but the decomposition was accompanied by considerable tar-formation, so that only small amounts of crystalline product could be isolated from the black and viscous liquid.

Reduction of the nitrosamine with zinc and hydrochloric acid was more successful, and was conducted thus: 10 grams of nitrosamine was suspended in water with 20 grams of zinc-dust. While stirring (mechanically), 75 cc. of strong hydrochloric acid was added from a separatory funnel, at such a rate that the temperature did not exceed 50°. When action was at an end, the liquid was treated with ammonium chloride, made alkaline with ammonia (using enough to hold the zinc in solution), and extracted with ether. The residue from the evaporation of the ether was taken up in a little dilute sulphuric acid, the liquid digested with animal charcoal, and crystallized. There were obtained 4.2 grams of the sulphate, corresponding to 37 per cent. As several trials resulted no better than this, it was decided to isolate the methylated base as such, without intermediate formation of the nitrosamine.

Procedure for Methylation of p-Aminophenol, with Final Experimental Results—

Condensation—This operation was conducted as described on page 25, paragraph (a).

Reduction—Transfer the solution to a beaker, into which is

[89] Noelting and Boasson, *Ber.*, 10, 795 (1877); Weyl, "Methoden", I, 219 (1911).

[90] Weyl, *l. c.*; Backer, *Rev. trav. chim.*, 32, 39.

[91] Geuther, *Annal.*, 128, 151 (1863); Stoermer, *Ber.*, 31, 2523 (1898).

[92] Henriques, *Ber.*, 17, 2671 (1884).

suspended a mechanically operated stirrer, and a thermometer; the beaker is supported on a plate above a bunsen burner. Weigh out 1 to 1.5 times as much zinc-dust as was taken of p-aminophenol, and introduce a portion of it into the beaker. Warm to about 50° a volume of 40-50 per cent sulphuric acid equal to that of the condensation liquid, and add it all at one time. While keeping the stirrer in rapid motion, add the zinc steadily and in small portions with sufficient rapidity that the solution is continually filled with gas-bubbles. Raise the temperature as quickly as possible to 70°-80°; this is much assisted by adding the zinc in larger portions at first. Keep the temperature near 80° by application of heat, until all the zinc has been added, and has dissolved. The liquid will be entirely clear and colorless, except for a small amount of insoluble matter from the zinc.

Removal of Unaltered p-Aminophenol—

Almost neutralize the liquid with sodium hydroxide, add sodium acetate, transfer to a capacious Erlenmeyer flask, and cool. Add a slight excess of benzaldehyde (3 or 4 grams for each 10 grams of p-aminophenol hydrochloride taken initially should be ample), and shake the stoppered flask. After the benzylidine-p-aminophenol has separated, filter it off, and wash with water. It may be treated as outlined on page 38 for recovery of benzaldehyde and p-aminophenol hydrochloride.

Isolation of N-Methyl-p-aminophenol as Sulphate—

Transfer the filtrate to a distillation-flask, and distil in steam until all excess of benzaldehyde is removed. Concentrate the liquid nearly to separation of salts, cool, add ammonium chloride, and then strong ammonia until the precipitated zinc redissolves. Extract the alkaline liquid four or five times with ether, which is then distilled off. Take up the residue in enough 40 per cent sulphuric acid to establish distinct acidity, and cool the liquid strongly. It should set to a stiff magma containing crystals of the sulphate. Filter, and wash the crystals with alcohol. Concentrate the filtrate to obtain a further crop of the sulphate. Digestion with good animal charcoal will assist the crystallization by elimination of tarry material. These crystallizations may

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cause some trouble, due to the rather viscous nature of the liquid, and to the presence of impurities which appear to retard crystal-formation.

Additional solid material may be obtained from the final mother-liquor by evaporation to pastiness, and extraction with alcohol. A light gray powder is thus obtained (as a residue insoluble in alcohol), which contains some methyl-p-aminophenol sulphate, but is evidently composed largely of some other substance, which is very soluble in water. This material has usually given the nitrosamine reaction, and with mercuric acetate developed a strong blue color (see page 28). It cannot easily be crystallized, because of its high solubility. Benzoylation of some of this substance yielded a product which melted at 132°-134°. Recrystallization of the main product affords a separation of the methyl-p-aminophenol sulphate from the more soluble compound. The mother liquors, however, always contain very appreciable quantities of the former, as may be demonstrated by precipitation as nitrosamine.

The ether extraction was a rather troublesome operation. The quantity of ammonia required to hold the zinc in solution renders the liquid somewhat bulky for hand-extraction; a mechanical shaker, or the continuous extraction device of Schwarz[98] would be of great assistance. During the extractions, there was a continual separation of a black foam-like material, which appeared to fill the ether layer completely; this was filtered off from time to time. The ether extracts were bright red in color. The complete removal of the coloring-matter requires many extractions, and is thought to be unnecessary, as methyl-p-aminophenol is very soluble in ether.

In the experiments tabulated below, aliquot portions were in most cases examined for uncondensed p-aminophenol after the condensation, and again after reduction; the extent of the reduction was determined by nitrosamine precipitation in another aliquot portion. The indicated yields are calculated on the basis of the weight of p-aminophenol hydrochloride actually subjected

[98] *Ber.*, 17, Ref. 402. (1884); Weyl, "Methoden", General Part, p. 131 (1909). p. 515 (1921).

to methylation, and not recoverable (compare Tables III, IV, V). The main portion of each experiment was treated for separation of the methylated base in the form of its sulphate. Freed from detailed data, and expressed only in nearest percentages, the results of the final experiments are as shown in Table VI.

TABLE VI.

Yield of cond. prod.	P. A. P. recovered after cond.	P. A. P. recovered after reduction	P. A. P. produced by hydrolysis	Yield based on nitrosamine	Yield based on sulphate	% P. A. P. acctd. for	% P. A. P. not acctd. for
—	—	26	—	36	—	—	—
—	—	35	—	47	23	66	34
67	29	40	11	47	37	68	32
77	21	32	11	39	28	59	41
77	21	25	4	30	31	48	52
—	—	33	—	—	28	52	48

From these results it may be concluded that

(a) About one-fourth of the p-aminophenol taken escapes condensation with formaldehyde.

(b) Hydrolysis of the condensation-product during reduction removes from the reaction an additional 10 per cent of p-aminophenol.

(c) The process is effective in methylating about 40 per cent of the p-aminophenol brought into reaction, as determined by precipitation of the secondary base as nitrosamine.

(d) The yield of the process, in terms of the secondary base itself, isolated as its sulphate, and referred to the amount of p-aminophenol actually subjected to methylation, is about 30 per cent. The method of isolation is insufficiently perfected.

(e) Of the total p-aminophenol initially taken, about 60 per cent can be accounted for, either as methylated base, or as unchanged p-aminophenol, which can be recovered without trouble.

(f) Approximately 40 per cent of the p-aminophenol initially taken enters into some side-reaction, and has not been accounted for.

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Identification of N-Methyl-p-aminophenol, produced from p-Aminophenol by the Method described above—

(1) *Nitrosamine* melted at 133° (corr.).

(2) *Dibenzoyl-derivative* melted at 174° (corr.).

(3) *Sulphate* (*Metol*) charred at 242°, and melted at 257°.

(4) *Nitrogen Determination* (*Kjeldahl*):

Found: 8.01
7.84 Average=7.9%
7.85

Calculated for $(HO.C_6H_4.NH.CH_3)_2H_2SO_4$: 8.14%

(5) Sulphate responded strongly to *mercuric acetate test.*

(6) A photographic film was developed by a solution containing a little of the sulphate, sodium sulphite, and sodium carbonate.

IV. Summary

(1) The available methods for conversion of the condensation-products of p-aminophenol and formaldehyde into N-methyl-p-aminophenol have been reviewed, and applied experimentally.

(2) The reduction of N-methylene-p-aminophenol (produced by condensation of p-aminophenol with formaldehyde in alkaline solution) by zinc-dust and sulphuric acid has in particular been subjected to investigation, and the course of the reaction has been studied.

(3) It has been found that the condensation of formaldehyde and p-aminophenol in alkaline solution is from 70 to 85 per cent complete; that during reduction by zinc and acid a further 10 per cent of the initial p-aminophenol is freed by hydrolysis of the condensation-product; that about 40 per cent of the p-aminophenol which actually enters the reaction as methylene-p-aminophenol, and is subjected to reduction, is methylated. The unchanged p-aminophenol may be recovered after removal from the solution as benzylidine-p-aminophenol after the reduction.

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